In the claims:

Please amend claims 39-43 under the provisions of 37 C.F.R. §1.121(b) by deleting the bracketed materials and inserting the underlined materials as follows:

--39.	(Amended) A pharmaceutical composition which comprises the CD4-IgG2 chimeric heterotetramer of claim [36, 37 or] 38 in an amount effective to inhibit HIV infection of a CD4+ cell and a pharmaceutically acceptable carrier.--
C1 --40.	(Amended) A composition of matter comprising the CD4-IgG2 chimeric heterotetramer of claim [36, 37 or] 38 and a toxin linked thereto.--
C2 --42.	(Amended) A diagnostic reagent comprising the CD4-IgG2 chimeric heterotetramer of claim [36, 37 or] 38 and a detectable marker linked thereto.--

REMARKS

Claims 30-35 and 38-43 are pending in this application. By this Amendment, claims 39, 40 and 42 have been amended. Therefore, upon entry, claims 30-35 and 38-43 are under examination.

Claims 39, 40 and 42 are amended to delete the dependency of previously cancelled claims 36 and 37. Accordingly, there is no issue of new matter and applicants respectfully request the entry of this Amendment.

The Examiner objected to claims 39-43 as being improperly dependent upon cancelled claims 36 and 37. In response, applicants have amended claims 39, 40 and 42 so that they are dependent on claim 38

since claim 41 is dependent on claim 40 and claim 43 is dependent on claim 42. Accordingly, they are now properly dependent on claim 38.

§112/101 Rejections

The Examiner objected to the specification and claims 31-33 and 39-41 under 35 U.S.C. §112, first paragraph, and rejected claims 31 and 39 under 35 U.S.C §101. The Examiner alleged that the current specification provides enablement only of the production of the peptides of the invention and their use in vitro. The Examiner alleged that no evidence of in vivo utility is presented, nor has the applicability of the in vitro test results to the use of the claimed protein in vivo been established. The Examiner asserted that there is sufficient reason to doubt that applicants' invention has utility in vivo. The Examiner alleged that the ability to inhibit binding and infection of CD4+ cells by HIV in culture is insufficient to establish a practical utility for applicants' invention as claimed. The Examiner asserted that it is clear from the specification as filed as well as the claims themselves that applicants intend the invention to be used as a therapeutic, administered to patients as an antiviral. The Examiner stated that the skilled artisan would not accept the inhibitory effect seen in cells in vitro as being predictive or correlative of an in vivo function for applicant's invention.

The Examiner stated that enablement of the current specification as filed is not commensurate in scope with claims to CD4-1g chimeric protein linked to toxins of any sort, for reasons cited in the previous Office Action at the paragraph bridging pages 2-3. The Examiner stated that applicants seem to have misread the original objection, as careful examination of such reveals that the Examiner was making the point that, as now admitted by applicants,

toxins are not useful as diagnostic reagents. The Examiner stated that applicants arguments that the claimed toxins are enabled are not found persuasive for reasons cited above.

In response, applicants respectfully traverse the Examiner's rejection.

Applicants draw the Examiner's attention to the Overview of Legal Precedent Governing the Utility Requirement issued by the U.S. PTO, on December 22, 1994 (hereinafter "Legal Precedent"). In the Legal Precedent, the Commissioner states that for therapeutic or pharmacological utility, if applicant's "asserted utility is credible, there is no basis for an Examiner to challenge such a claim on the grounds that it lacks utility." Legal Precedent, page 2 (emphasis in original). In determining whether the asserted utility is credible, the Examiner "should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis." Legal Precedent, page 4 (emphasis in original). The evidence provided by applicants is to be considered sufficient "if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." Legal Precedent, page 6 (emphasis in original). The Legal Precedent provide that only where the asserted utility is "'incredible in view of contemporary knowledge'" (Legal Precedent, page 4) should the Examiner challenge the assertion and then the Examiner must provide "evidentiary support" for the rejection. Legal Precedent, page 5.

Applicants maintain that the utility of the claimed invention has been sufficiently established and therefore the above ground of rejection is improper. Applicants have asserted a credible utility for the claimed invention and the Examiner has not provided any

evidence[1] to rebut applicants' assertion. Further applicants have demonstrated that representative examples of the claimed invention have the ability to inhibit binding and infection of CD4 cells by HIV. Applicants maintain that the "asserted utility is credible", that the assertions of applicants have a "reasonable scientific basis", and that the evidence provided by applicants is to be considered sufficient since it would lead a "person of ordinary skill in the art to conclude that the asserted utility is more likely than not true."

Regarding the Examiner's statement that "the current specification as filed is not commensurate in scope with claims to CD4-Ig chimeric proteins linked to toxin of any sort", August 9, 1994 Office Action, page 4, lines 9-10, applicants disagree.

Applicants maintain that a person of ordinary skill in the art would know how to make such toxin conjugates. In fact, applicants have described methods to synthesize such conjugates. See Specification, page 23, lines 19-30. Accordingly, in view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw this ground of objection.

§103 Rejections

The Examiner rejected claims 30-35 and 38-43 under 35 U.S.C. §103 as obvious over U.S. Patent Number 5, 116,964 either or taken with

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[1]It is stated in the Guidelines for Examination of Applicants for Compliance with the Utility Requirement issued by the PTO on December 22, 1994, page 4, that "Whenever possible, the Examiner must provide documentary evidence that supports the factual basis of a prima facie showing of no utility (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents)." The Examiner has not provided the documentary evidence in this case.

applicants admissions in the specification of the state of the prior art for reasons of record in the previous Office Action at pages 4-5. The Examiner stated that applicants' argument that the '964 patent teaches away from the claimed invention at column 7 has been fully considered but is not deemed persuasive. The Examiner stated that the cited portion of the patent is directed to a specific limitation of the claimed invention, which limitation was included to avoid the prior art. The Examiner stated that upon examination of the patent as a whole, one finds multiple teachings toward the currently claimed invention, for example at Column 5, lines 1-5 and 48-55, and Col. 30, lines 54-66. Thus, in summary, the Examiner stated that the Capon patent taken as a whole teaches strongly toward the use of CD4-Ig chimeras for the purpose of targeting HIV infected cells.

In response, applicants respectfully traverse the Examiner's rejection.

U.S. Patent No. 5,116,964 teaches bi-specific antibody approaches and does not teach the applicants' claimed invention which is a mono-specific molecule. The below citations by the Examiner fully support the applicants' position:

> "For example, a hybrid immunoglobulin consisting of <u>one LHR-IgG chain</u> and <u>one CD4-IgG chain</u> can be used to target CD4-IgG to tissues infected by viruses such as the human immunodeficiency virus (HIV)." Column 5, lines 1-5.

> "A particular multichain fusion of this sort is one in which the variable region of one immunoglobulin chain has been substituted by the <u>ligand binding region of a first receptor such as CD4</u> while the variable region of another immunoglobulin chain has been

> substituted by a binding functionality of the LHR, both immunoglobulin chains being associated with one another in substantially normal fashion." Column 5, lines 48-55.
>
> "For example, a hybrid immunoglobulin consisting of one LHR-IgG chain and one CD4-IgG chain can be used to target CD4-IgG to tissues infected by the viruses such as the human immunodeficiency virus (HIV). Because this hybrid binds to endothelial tissue not only in lymph nodes, but in secondary lymphoid organs such as Peyner's patches and in the brain, it may be used for delivery of CD4-IgG across the blood-brain barrier for the treatment of HIV-related dementia. Similarly, a heterotetrameric immunoglobulin having a LHR-ricin-or CD4ricin-immunoglobulin as described herein is used to deliver a toxin such as ricin to desired tissues." Column 30, lines 54-66.

Contrary to the Examiner's allegation, every time CD4 is stated, it is always associated with a second specificity. Accordingly, applicants maintain that the U.S. Patent No. 5,116,964 does not render the claimed invention obvious and applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

The Examiner rejected claims 30-35 and 38-43 under 35 U.S.C. §103 as being unpatentable over WO89/02922 in view of Capon et al. (Nature) for reasons cited in the previous Office Action at pages 5-6. The Examiner stated that applicants argument that neither cited reference teaches the inclusion of the entire hinge domain of the IgG2 moiety is not persuasive. The Examiner stated that the '922 publication clearly discloses the use of the entire 1g constant region, for example at page 13 in the discussion of an IgG1 adhesion. The Examiner stated that the ordinary artisan is well aware the entire constant region of a immunoglobulin comprises

the entire hinge domain as well as the "remaining" (carboxyl terminus) portion of the molecule. The Examiner stated that the '922 publication also clearly teaches the use of IgG2, as cited in the previous Office Action.

The Examiner stated that the advantages of using IgG2 pointed out by applicants in their traversal of the rejection are properties which were known to be associated with IgG2 prior to the current invention, therefore, the claimed invention merely uses the suggestions of the prior art to make an obvious combination for its known and expected properties. The Examiner stated that applicants argument that the cited references do not teach conjugation with a toxin are not persuasive in view of the quotation from the previous Office Action, above, the reference clearly and directly suggests conjugation to a toxin.

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the heterotetramers of the subject invention would not have been obvious to one of ordinary skill in the art over '922 and Capon et al. In responding to the applicants' comment that the non-obviousness of the homodimer would not be obvious over '922 and Capon et al., the Examiner stated that on page 13 of '922, there is disclosure of the entire Ig constant region which comprises the entire hinge domain and therefore, '922 will make the applicants' homodimer obvious. Applicants respectfully disagree. The entire Ig constant region includes the CH1 domain (illustrated on page 1 of '922, the fourth molecule). This is different from the applicants' homodimer which does not contain the CH1 domain. Applicants maintain that the entire Ig constant region would not render the applicants' homodimer which does not contain the CH1 domain obvious. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the August 9, 1994 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 30-35 and 38-43.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Please be advised that applicants' undersigned attorney's new address, telephone number, and facsimile numbers as of October 31, 1994 are as follows:

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No fee, except the $435.00 fee for a three-month extension of time which the undersigned attorney authorizes the Patent Office to charge to Deposit Account No. 03-3125, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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